Protocol #1304-1224 RAC Presentation

E10A (Endostatin Adenovirus) for the Treatment of Recurrent/Metastatic Squamous Cell Carcinoma of the Head & Neck

George Yoo, M.D., FACS

PI, Head and Neck Surgery, Karmanos Cancer Center & Wayne State University
(Disclosure: Consultant Marsala Biotech)

George Thomas, Ph.D.

CEO, Marsala Biotech Inc. (Disclosure: employee Marsala Biotech)

Nancy Stewart, Ph.D.

Director of Clinical Development, Marsala Biotech Inc. (Disclosure: employee Marsala Biotech)

Bob Choy, Ph.D.

Clinical Research Scientist, Marsala Biotech Inc. (Disclosure: employee Marsala Biotech)

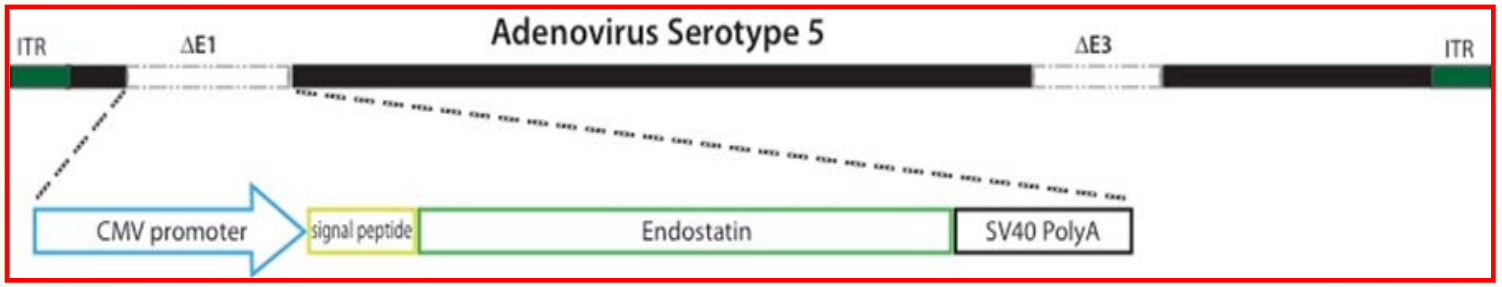
marsalabiotech

Outline

- **Overview: Endostatin & E10A**
- **Summary: protocol**
- **Key points trial design**
- **Biological activity - E10A**

Overview: Endostatin & E10A

- **Endostatin**
  - Inhibits angiogenesis
    - Affects endothelial cell viability & movement: multiple pathways
  - Arrest cell cycle in endothelial cells
  - Induces apoptosis genes in proliferating endothelial cells
- **E10A:** Non-replicating Adenovirus+Endostatin



  - Wild-type human endostatin cDNA
  - Sustained serum endostatin levels
    - Intra-tumoral E10a (5-7 days) versus IV endostatin (~10 hours).

marsalabiotech

E10A Proposed Phase III Protocol

Objectives: To demonstrate the benefit of E10A in treating patients with recurrent/unresectable & metastatic head and neck cancer when combined with chemotherapeutic agents. [N= 400 subjects]

Treatment: Subjects will be randomized 1:1

- Group-1: E10A group: E10A + chemotherapy
- Group-2: Chemotherapy only

E10A: Intratumoral injection of 1.0×10^{12} VP (VP = viral particles)
Day 1 & 8 every 21 days.

Chemotherapy: Acceptable chemotherapy combinations

a. 5FU + cisplatin or carboplatinum
b. 5FU + cisplatin or carboplatinum + erbitux
c. Taxane +cisplatin or carboplatinum + with/without 5FU

marsalabiotech

Trial design: Key points

- **Justification for proposed E10A trial**
- **E10A & Chemo**
- **Recurrent & metastatic HN cancer**
- **Statistical design**
- **Safety profile of E10A**

E10A - Phase I Clinical Trial

Methods:

- 15 patients (head/neck, colon, & cervical cancers)
- Intra-tumoral injection of E10A, once a week for 2 weeks.
- Dose escalation:
  - 4 groups ($1x10^{10}$, $1x10^{11}$, $5x10^{11}$, or $1x10^{12}$ VP)

Outcome:

- E10A treatment was well tolerated.
- No dose-dependent toxicity.
- No severe adverse events were observed.
- Minor adverse events:
  - Local reactions: local pain or swelling.
  - Fever

E10A - Phase II Clinical Trial

Study: Open Label Phase-II Clinical trial of E10A in combination with Paclitaxel + Cisplatin in Patients with Head and Neck Carcinoma-II

Subjects: Patients with local advanced or metastatic head and neck squamous cell carcinoma or nasopharyngeal carcinoma

Study Groups:

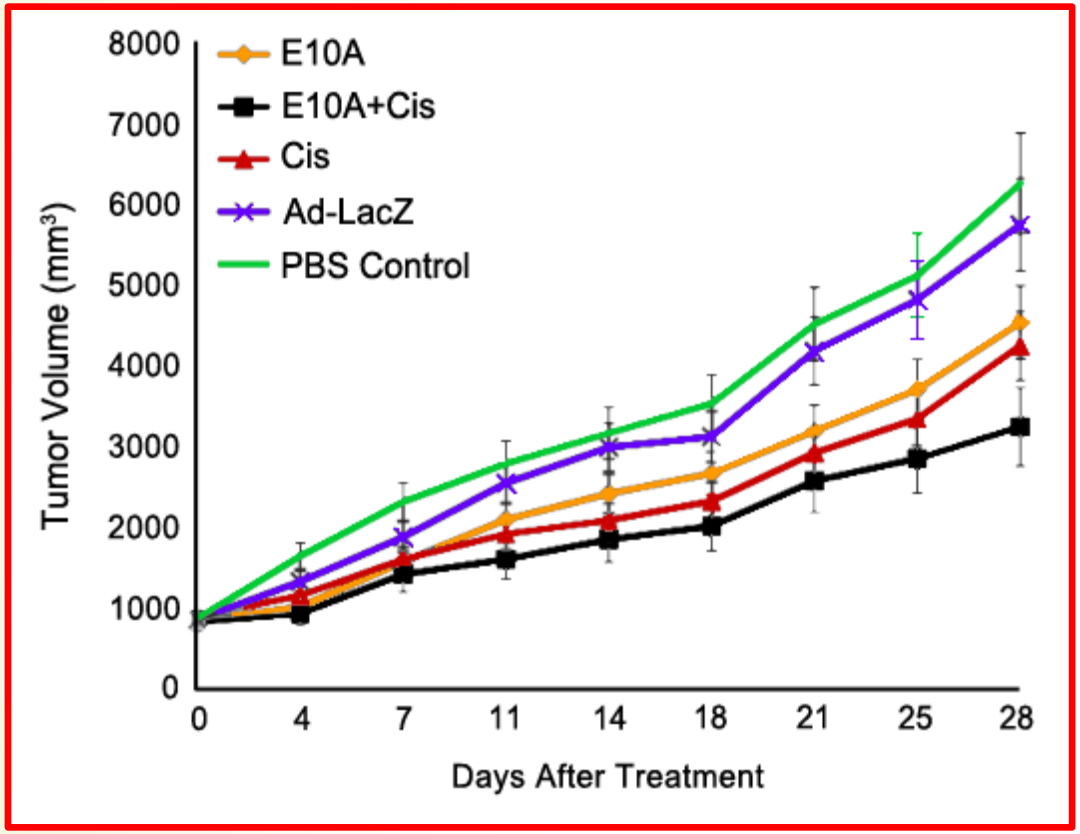
- E10A (days 1 & 8) + Chemo (Paclitaxel: day 3 + Cisplatin days 3-5)
- Chemo alone (Paclitaxel: day 1 + Cisplatin days 1-3)

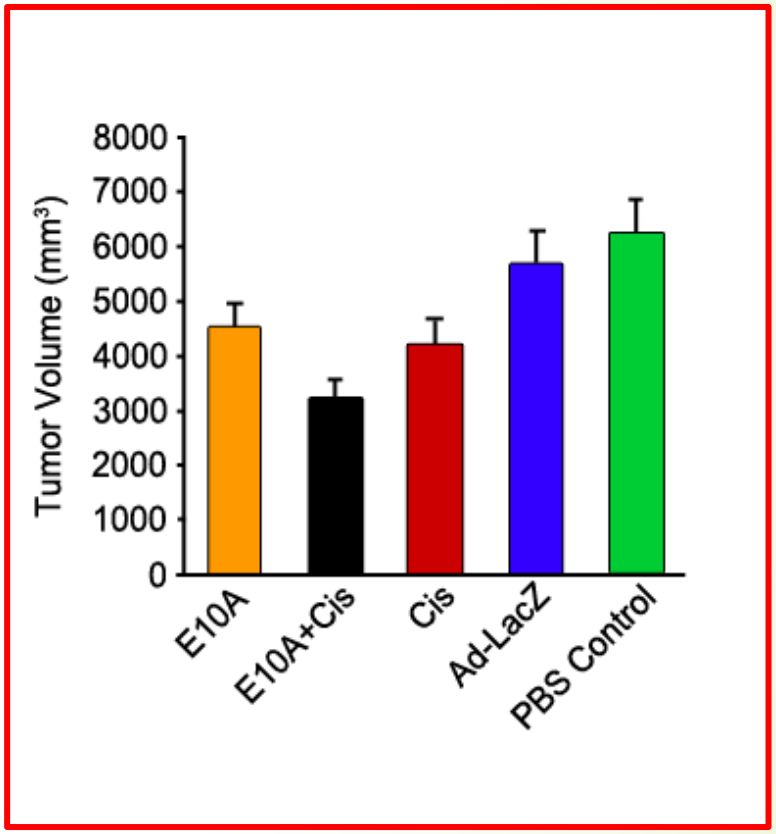
Outcome:

	E10A + Chemo	Chemo only	% Benefit	P
Median Progression Free Survival (months)	**6.9**	**3.6**	**92%**	**<0.01**
Median survival (months)	**18.8**	**14.3**	**31%**	**NS**

Synergy: E10A + Chemotherapy

Human hypopharyngeal cancer xenografts in BALB/c mice model



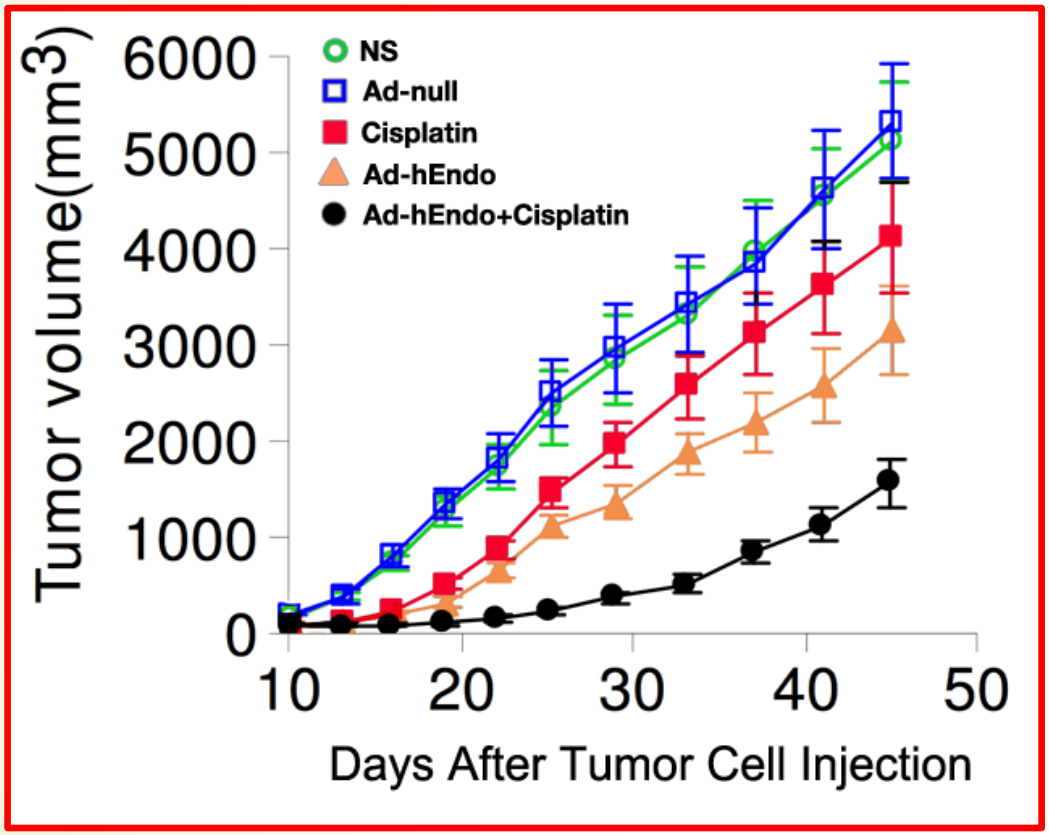


Adhim, Z. et al., 2011. *Cancer gene therapy*, 19(2), pp.144–152.

marsalabiotech

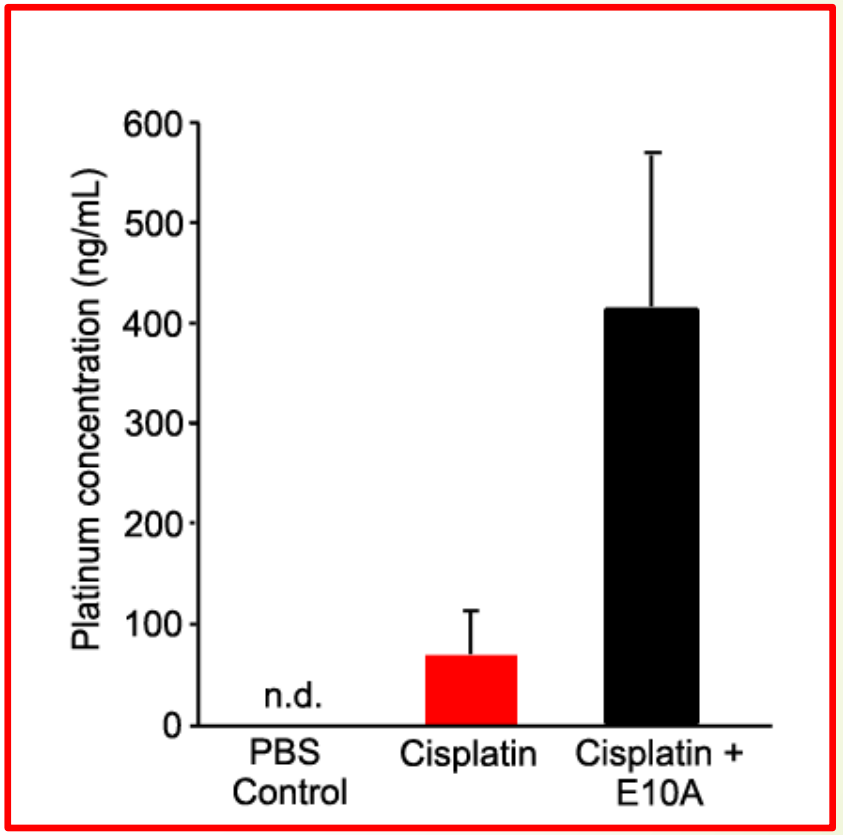
Synergy: E10A + Chemotherapy

Lung cancer mouse model



Bai, R.Z. et al., 2009. *Journal of experimental & clinical cancer research : CR*, 28, p.31.

Intratumoral Cisplatin concentration



Adhim, Z. et al., 2011. *Cancer gene therapy*, 19(2), pp.144–152.

marsalabiotech

Recurrent/unresectable or metastatic head and neck cancer (HNCa)

- **Poor outcomes**
  - Median survival: 5 -10 months
    - Worden, FP et al, Cancer 2006.
- **No existing targeted therapy**
- **Previous chemotherapy:**
  - No chemo:
    - Newly diagnosis with distant metastasis
    - Recurrent: Surgery and/or radiation alone
  - Previous chemo curative setting
    - Induction chemo or adjuvant Chemo-RT
  - Chemo for recurrent and/or metastasis
    - None vs. ≥1 course chemo

marsalabiotech

Treatment for recurrent/unresectable or metastatic HNCa

- **NCCN guidelines**
  - Recurrent/unresectable
    - Chemotherapy
    - Re-irradiation ± chemotherapy
  - Distant metastasis: Chemotherapy
- **Re-irradiation**
  - Eligibility Criteria:
    - "Patients not suitable for surgery or radiotherapy"
  - NCCN: Re-irradiation ± chemotherapy is option
    - "highly selected group of patients treated in centers where there is high level of expertise"

marsalabiotech

Chemotherapy Regimens
Recurrent/unresectable & Distant Metastasis

- **NCCN – combination chemo**
  - 5-FU + cisplatin
  - 5FU + cisplatin/carboplatinum + erbitux
  - Docetaxel/paclitaxel + Cisplatin/carboplatin
  - Cisplatin + erbitux
- **This protocol**
  - 5FU + cisplatin/carboplatinum
  - 5FU + cisplatin/carboplatinum + erbitux
  - Taxane +cisplatin/carboplatinum +/- 5FU

Chemotherapy: Recurrent/unresectable & Distant Metastasis

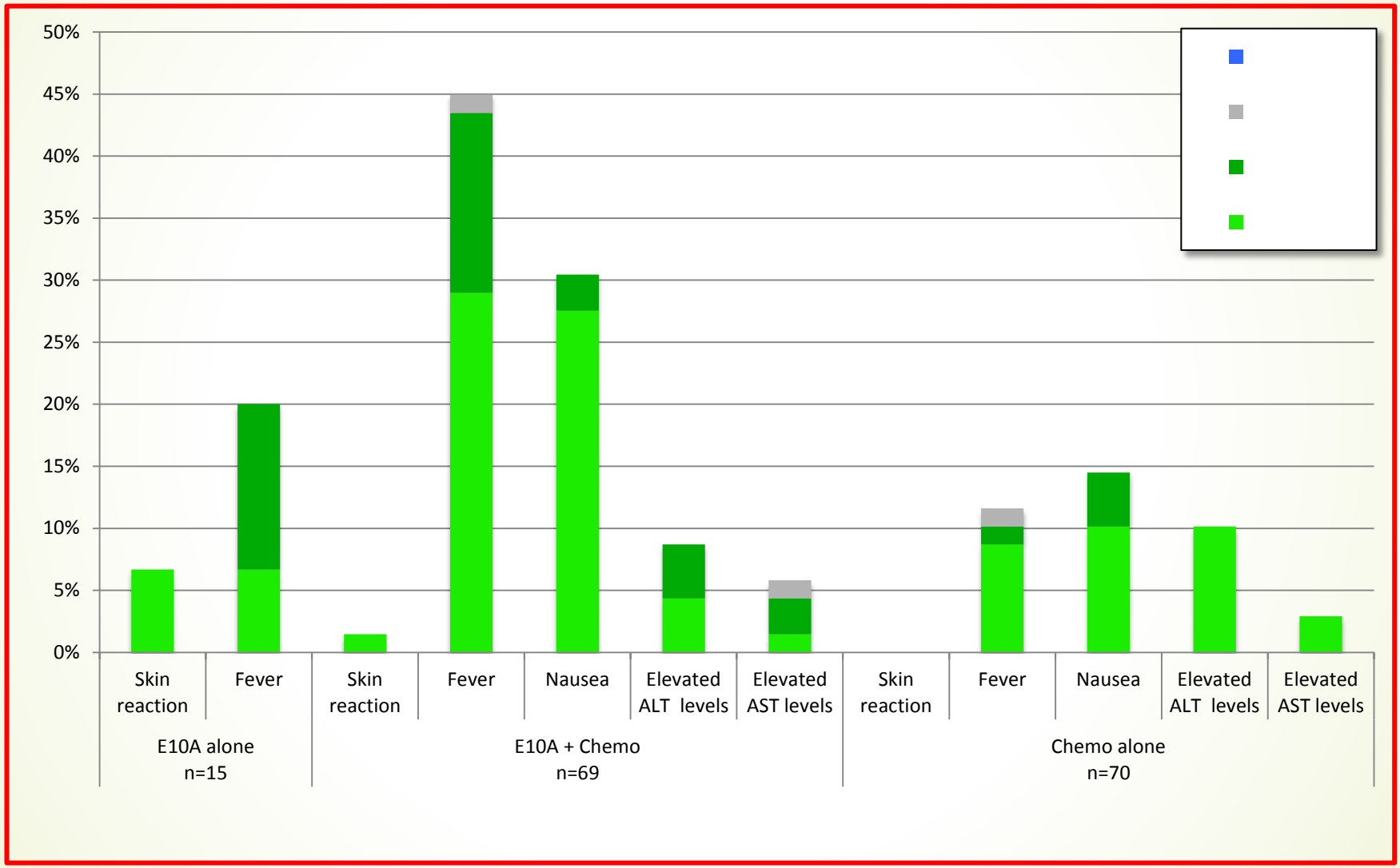
- **No definitive chemotherapy standard**
  - NCCN: "The choice of chemotherapy should be individualized based on patient characteristics"
- **Choice: individualized for patient**
  - Previous chemotherapy
  - General health of patient
- **Three chemotherapy options**
  - Standard therapy: a choice of 1 of 3
  - Stratification for chemotherapy planned

marsalabiotech

Statistical design

- **Randomization will be stratified**
  - ECOG Performance Status
  - Chemotherapeutic regimen
  - First time recurrence versus refractory
  - Presence or absence of distant metastasis
- **Adequately powered trial**
  - Median OS of 6 months in the control arm
  - Hazard ratio of 0.71
  - 88.1% power
  - One-sided significance level, alpha of 0.025
  - Assuming exponential survival

Phase II Clinical Trial - Adverse Reactions



Liver Toxicology

- **Preclinical animal toxicology:**
  - No abnormal hepatic function
  - No abnormal liver histology
- **Phase I and Phase II clinical trials**
  - No significant liver adverse effects
- **Proposed Phase III trial**
  - Liver function and toxicity: strictly monitored
    - Treatment & follow-up phases
  - Adverse events monitoring

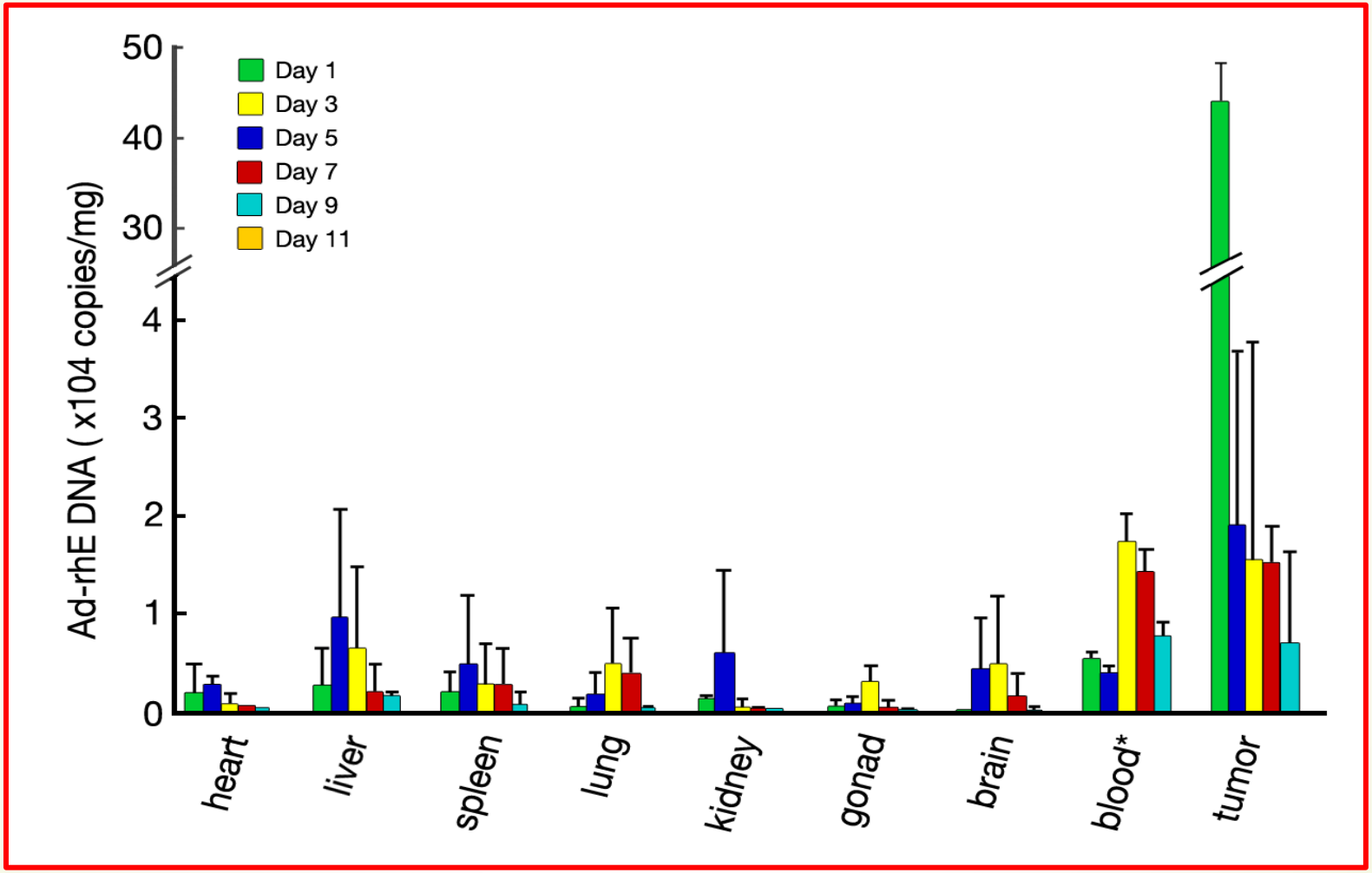
marsalabiotech

Spread and Vector Shedding of E10A

- **Local** - viral shedding: FQ-PCR swab
  - Injection site
    - Residual E10A up to 3 days & none detected after 4days
    - The residual quantity is related to dose.
  - Pharynx
    - No E10A is detected at the pharynx 3 days after dosing.
- **Blood Levels**
  - Absorption into blood appears: 4 and 8 hrs.
  - The absorption amount: not related to the dose
  - No E10A was detected after 7 days: all subjects

Tissue Distribution After Intratumoral Injection in Mice

B16 murine melanoma cells: BALB/c mice



He GA et al, Life Science, 2005

Safety of non-replicating adenovirus

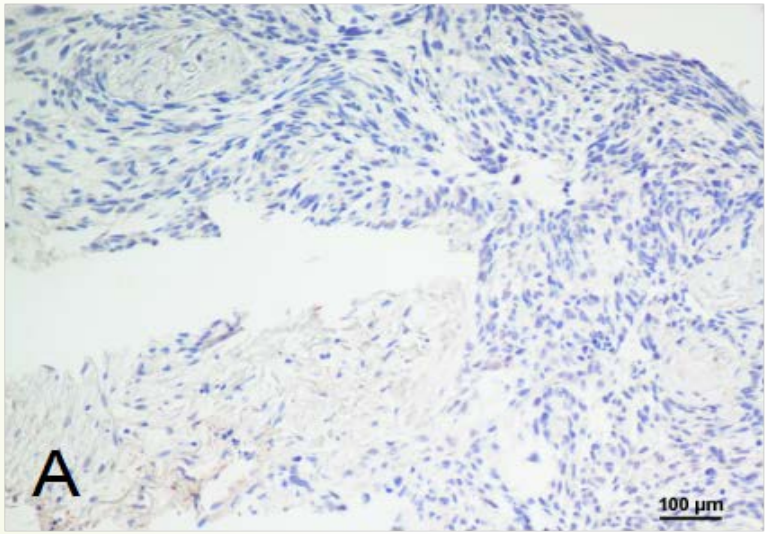
- N = 9 clinical trials (published data)
  - Ad5 totals trials = 23
- N = 873 patients
- Vectors:
  - Ad5ΔE1E3-CMV, Ad5ΔE1-CMV
  - Ad5ΔE1E3-RTS
  - Ad5ΔE1E3-RSV, Ad5ΔE1a-RSV
  - Ad5ΔE1-muPPE
- No systemic toxicity related to Ad5
  - Local injection toxicity
- No safety issues with intratumoral injections

marsalabiotech

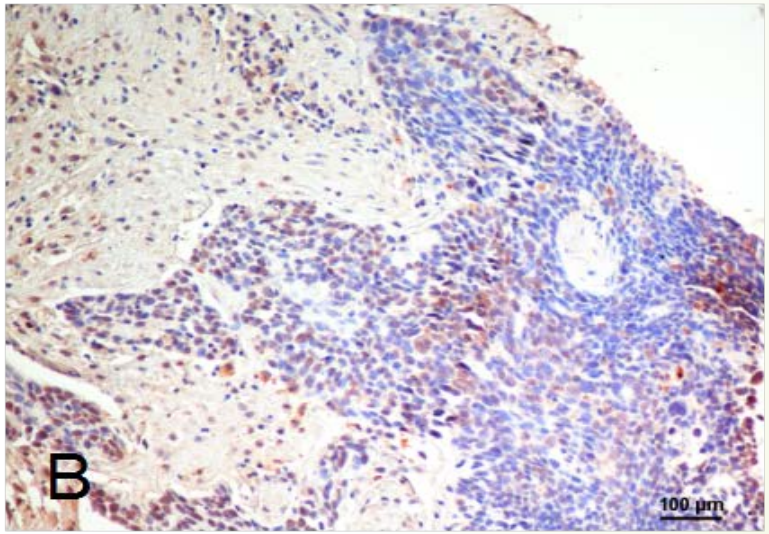
Phase II: Tumor tissue response-E10A

- **Tumor tissues:**
  - Six cases – E10A group: before/after injection
- **Endostatin Expression:**

A) Before Treatment



B) After Treatment

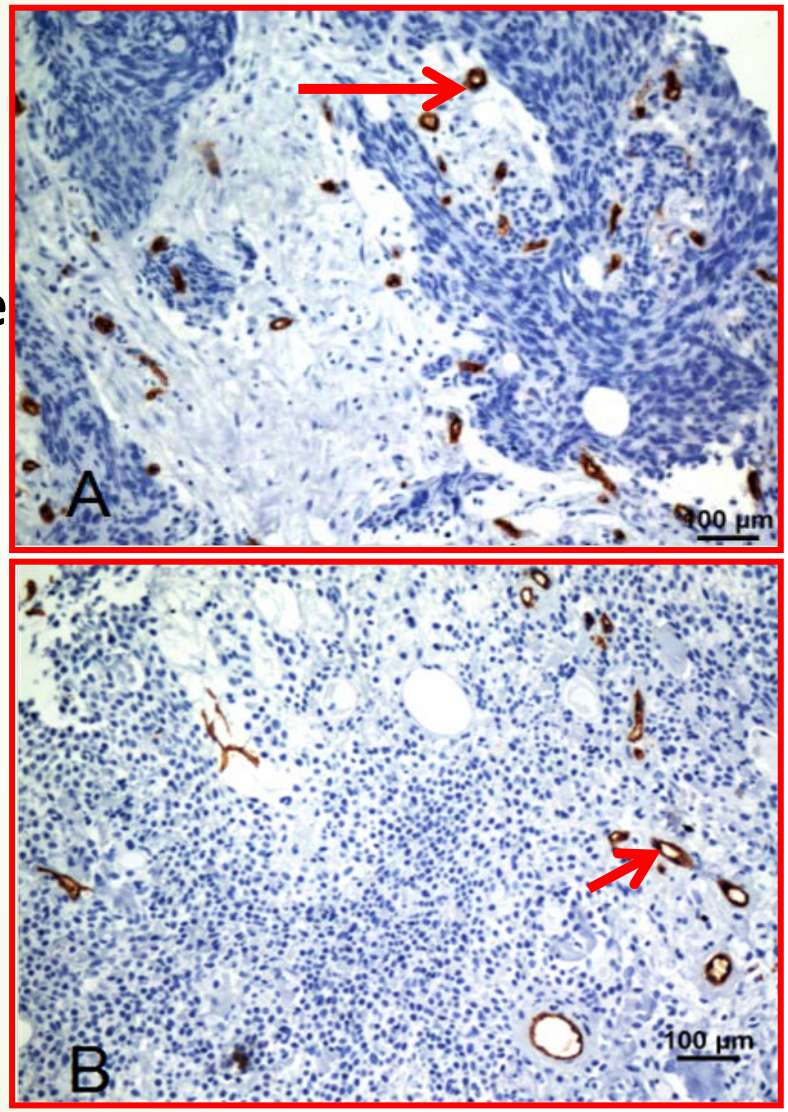


Unpublished

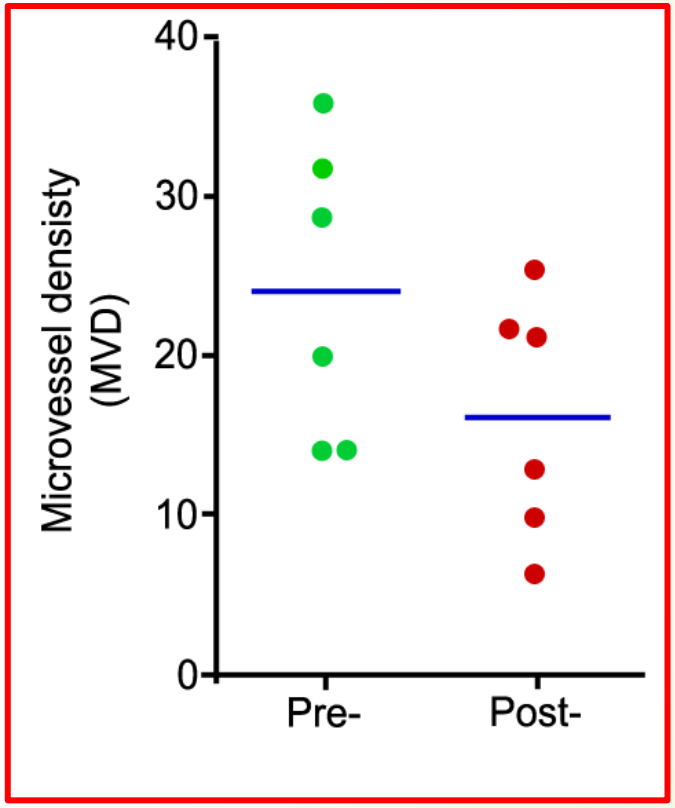
CD34 Expression & MVD: E10A

Before

After



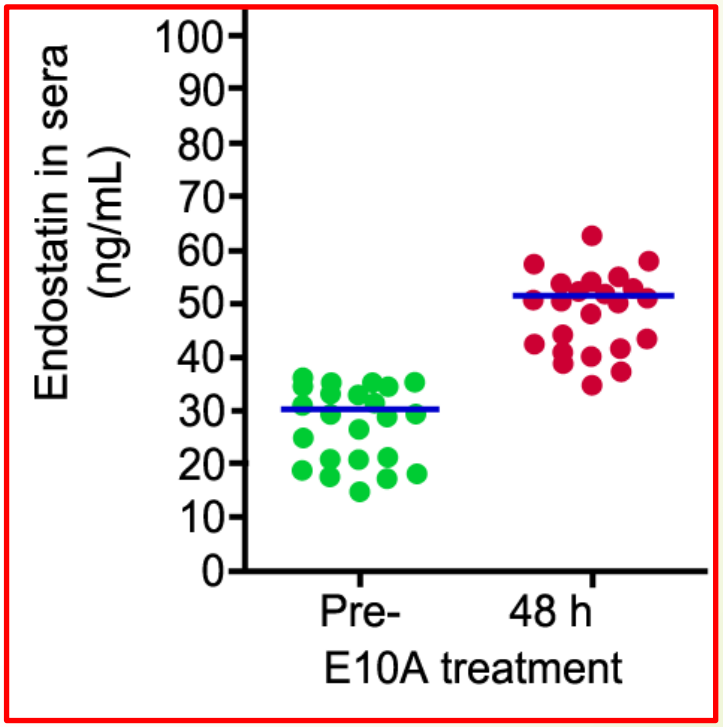
Microvessel Density



Unpublished

E10A Transgene Expression: Serum

- **Injection:** E10A on Days 1 and 8
- **Endostatin serum concentration: ELISA**
  - First cycle: Before and after
  - Second cycle: Before and after
- **Concentration of serum endostatin**
  - 20 patients
  - Increased 8-12hrs post injection
  - Peaked at 3-5 days post injection
  - Returned to baseline after 14
  - Remained elevated until 28 days



marsalabiotech

Thank You

- Detailed response
  - Drs. Koch, Strome & Dresser
- Clarification: application and consent
- Discussion